Hypothyroidism might be related to breast cancer in post-menopausal women

Kuijpens, J.L.; Nyklicek, I.; Louwman, W.J.; Weetman, A.P.; Pop, V.J.M.; Coebergh, J.W.W.

Published in:
Thyroid

Publication date:
2005

Document Version
Publisher's PDF, also known as Version of record

THYROID
Volume 15, Number 11, 2005

Hypothyroidism Might Be Related to Breast Cancer in Post-Menopausal Women

Johannes L.P. Kuijpens,[1] Ivan Nyklíčtek,[2] Marieke W.J. Louwman,[1] Tony A.P. Weetman,[3] Victor J.M. Pop,[4] and Jan-Willem W. Coebergh[1,5]

An association between breast cancer and thyroid (autoimmune) diseases or the presence of thyroid peroxidase antibodies (TPOAb; a marker of thyroid autoimmune disease) has been suggested. However, little is known about whether women with thyroid (autoimmune) diseases are at increased risk for developing breast cancer. This cross-sectional and prospective cohort study investigated whether the presence of TPOAb or thyroid dysfunction is related to the presence or development of breast cancer. An unselected cohort of 2,775 women around menopause was screened for the thyroid parameters thyrotropin (TSH), free thyroxine (FT_4), and TPOAb during 1994. Detailed information on previous or actual thyroid disorders and breast cancer, and on putative factors related to breast cancer and thyroid disorders, was obtained. Clinical thyroid dysfunction was defined by both abnormal FT4 and TSH, and subclinical thyroid dysfunction by abnormal TSH (with normal FT4). A TPOAb concentration $\geq$ 100 U/ml was defined as positive ($TPOAb^+$). The study group was linked with the Eindhoven Cancer Registry to detect all women with (*in situ*) breast cancer (ICD-O code 174) diagnosed between 1958 and 1994. Subsequently, in the prospective study, all women who did not have breast cancer in 1994 (n = 2,738) were followed up to July, 2003, and all new cases of (*in situ*) breast cancer and all cancer-related deaths were registered. Of the 2,775 women, 278 (10.0%) were $TPOAb^+$. At the 1994 screening, 37 women (1.3%) had breast cancer. TPOAbs were (independently) related to a current diagnosis of breast cancer (OR = 3.3; 95% CI 1.3–8.5). Of the remaining women, 61 (2.2%) developed breast cancer. New breast cancer was related to: (1) an earlier diagnosis of hypothyroidism (OR = 3.8; 95% CI 1.3–10.9); (2) the use of thyroid medication (OR = 3.2; 95% CI 1.0–10.7); and (3) low FT4 (lowest tenth percentile: OR = 2.3; 95% CI 1.2–4.6). In the first 3 years follow up, the relationship between FT4 and log-TSH was disturbed in women with a new breast cancer diagnosis. The presence of TPOAb was not related to breast cancer during follow-up. A direct relationship between thyroid autoimmunity and breast cancer is unlikely. Hypothyroidism and low-normal FT4 are related with an increased risk of breast cancer in post-menopausal women. Studies are needed to clarify the origins of this possible association.

Introduction

Breast cancer is a major public health problem, with a cumulative incidence of 9% for women in The Netherlands, accounting for 10,000 new patients annually (1). Apart from familial predisposition, occupational, and reproductive/hormonal factors (which have a weak association with breast cancer), and probably alcohol use of $\geq$3 drinks a day, no clinically important risk factors for breast cancer are known (2–4).

Together with the thyroid, human breast tissue shares the ability to take up circulating iodide (5), and a sodium/iodide symporter is expressed in lactation and in mammary tumors (6). Also, alterations of iodide metabolism exist in both the tumor and normal tissue of breast cancer patients (5). These studies suggest a possible association between breast cancer and alterations in iodine metabolism.

Moreover, a relationship between breast cancer and thyroid disorders (especially autoimmune thyroid disease) has been suggested: greater volumes of the thyroid were found in breast cancer patients (7,8), the prevalence of thyroid peroxidase antibodies (TPOAb, a marker for autoimmune thyroiditis) was increased (8–12), and various thyroid disorders were more prevalent (10,12). In addition, the presence of

[1]Comprehensive Cancer Center South (IKZ), Eindhoven, The Netherlands.
[2]Faculty of Social and Behavioural Sciences, Department of Psychology and Health, Tilburg University, Tilburg, and Research Unit of the Diagnostic Center, Eindhoven, The Netherlands.
[3]Department of Medicine, University of Sheffield, Sheffield, UK.
[4]Faculty of Social and Behavioural Sciences, Tilburg University, Tilburg, The Netherlands.
[5]Department of Public Health, Erasmus University Medical Center, Rotterdam, The Netherlands.

TPOAb might have a positive effect on the prognosis of women with breast cancer; women treated with surgery and who were positive for TPOAb showed a better prognosis than TPOAb-negative women (11). However, all of these studies were performed in selected groups of patients (women with either breast cancer or thyroid disorders) and did not study prospectively the incidence of breast cancer in relation to thyroid parameters (such as thyroid function testing or TPOAb) in an unselected cohort. Very few data are known regarding the question of whether women with thyroid dysfunction or TPOAb are at risk for the development of breast cancer. One older study was unable to show an increased incidence of breast cancer in patients with various thyroid disorders (12). Therefore, in an unselected cohort of women around menopausal age, we studied both cross-sectionally and prospectively whether: (1) the presence of TPOAb was associated with a diagnosis of breast cancer or with the development of breast cancer; and (2) subclinical or clinical thyroid dysfunction was more prevalent in women with breast cancer or was associated with the development of breast cancer, independently of known risk factors.

Subjects and Methods

Subjects

During 1994, all women aged between 47 and 54 years (n = 8,503; see Fig. 1) living in the city of Eindhoven were invited to participate in the Eindhoven perimenopausal osteoporosis study (EPOS, a study to estimate the prevalence of osteopenia and osteoporosis in perimenopausal women, and to assess determinants of low bone mineral density) (14,15). Informed consent was obtained from 5896 Caucasian Dutch women (73%). In an at-random chosen cohort of 2,775 women (47% of the participants), thyroid function and TPOAb testing were performed (Fig. 1).

Detailed gynecological (including obstetrical), endocrinological, and general medical histories, as well as the use of medication (including oral contraceptives and thyroid medication (thyroxine replacement therapy or the use of thyrostatica: carbimazol and strumazol), the use of alcohol, and smoking habits were determined by paramedical assistants. Venous blood samples for thyroid function testing were collected in Vacutainer tubes (8 ml). In a recent paper, the actual daily intake of iodine in the region was proved to be sufficient (16), whereas previously the daily intake of iodine had appeared to be low-normal (17).

The Eindhoven Cancer Registry was founded in 1955 and became part of the Comprehensive Cancer Center South in 1983. The registry covers the southeastern part of The Netherlands, a region with 2.3 million inhabitants, including the city of Eindhoven. The registry can be considered as being "complete" since the early 1970s. In the region, the national breast cancer screening program for women aged from 50 to 69 years was implemented in the early 1990s. About 80% of all women participate in this program, and all hospitals and the radiotherapy institutes in the region participate in the cancer registry. Breast cancer and *in situ* carcinoma of the breast are registered according to the International Classification of Diseases for Oncology (ICD): ICD-O code 174. In addition, the estrogen receptor status (positive or negative) was assessed in all women with breast cancer.

Thyroid parameters

Thyroid parameters were assessed by the measurement of free T4 (FT4; reference range 8–26 pmol/L; Abbott, North Chicago, IL), thyroid-stimulating hormone (TSH; reference range 0.4–6 mU/L; Abbott), and TPOAb (Autozyme Tab, Cambridge Life Sciences, Cambridge, UK). The coefficients of variation for FT4 were 6.8, 8.2, and 6.7% at concentrations of 6.4, 18, and 30 pmol/L, respectively; those for TSH were 9.8, 4.8, 3.9, and 3.1% at concentrations of 0.06, 0.75, 6.8, and 30 mU/L, respectively; and that for TPOAb was 9.6% at a concentration of 231 U/ml. Clinical thyroid dysfunction was defined by the presence of both FT4 and TSH concentrations outside the reference range, whereas subclinical thyroid dysfunction was defined by a TSH concentration outside the reference range, with FT4 within reference limits. The TPOAb assay was standardized according to the International Reference Preparation for anti-TPO MRC 66/387. A TPOAb concentration of >99 U/ml was defined as positive ($TPOAb^+$).

Analysis

In 1994, the study group (n = 2,775) was linked to the Eindhoven Cancer Registry to determine all women with previous (since 1958) or actual breast cancer or *in situ* carcinoma of the breast. Women with no diagnosis of breast cancer in 1994 were followed up to July, 2003, and were linked again to identify new cases of breast cancer (see Fig. 1). The incidence date (date of diagnosis) was noted. Also, all women who had died of cancer (all types) during follow up were registered.

Two separate analyses (both at a univariate and a multivariate level) were performed. During the first analysis, the relationship between breast cancer and putative determinants, including thyroid parameters and TPOAb, was studied cross sectionally. All women without a diagnosis of breast cancer at the time of screening were introduced in the second analysis to study prospectively the relationship between a new diagnosis of breast cancer and putative risk factors (including thyroid parameters and TPOAb).

Statistical analysis was performed by using SPSS-11. Univariate differences were determined using the Chi-square test. In addition, multiple logistic regression analyses were performed to examine whether thyroid-related and other hormonal factors were associated with breast cancer, independently of known risk factors. Factors with $p \leq 0.1$ in the univariate analysis, and factors known from the literature to

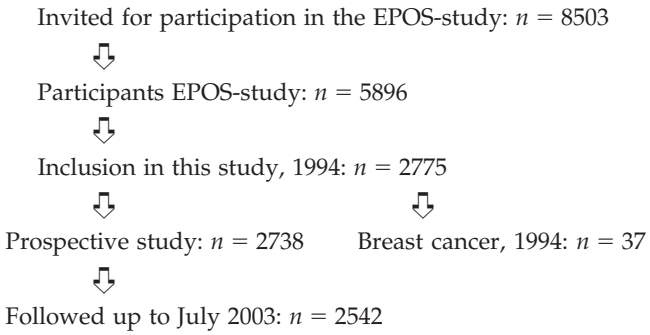

FIG. 1. Flowchart of inclusion and participation of women in this study.

be (possibly) related to breast cancer (positive family history, nulliparity, early menarche, and estrogen or alcohol use), were introduced into the model. Odds ratios (OR) with 95% confidence intervals (95% CI) were calculated. Apart from the subject's own informed consent for the cohort study, permission for linking up to the cancer registry was obtained from the medical supervisory committee of the Comprehensive Cancer Center South, Eindhoven.

Results

The characteristics of the 2,775 women are presented in Table 1. TPOAbs were present in 278 women (10.0%). The number of women with breast cancer during the study period as a whole was 98 (3.5%). Fifteen of these 98 women (15.3%) were $TPOAb^+$. $TPOAb^+$ women differed with regard to smoking habits and the use of alcohol (Table 1). The mean TSH concentration in $TPOAb^+$ women was significantly higher than in women without TPOAb (5.59 mU/L, SD = 11.14, versus 1.58 mU/L, SD = 2.66; *t* test, $t = -5.678$, $p < 0.001$); the mean FT4 concentrations in $TPOAb^+$ women were lower (14.3 pmol/L (SD = 4.2) versus 15.4 pmol/L (SD = 2.4; *t* test, $t = 6.234$, $p < 0.001$). Subclinical thyroid dysfunction was found in 7.3% of the women: 118 (4.6%) had decreased TSH and 69 (2.7%) increased TSH and 18 women (0.7%) had clinical thyroid dysfunction. Twelve showed over hypo- and 6 overt hyperthyroidism. Both (subclinical and clinical) thyroid dysfunction and the use of thyroid medication (thyroxine and thyrostatica) were more prevalent in $TPOAb^+$ women (Table 1).

Estrogen receptor status was known in 23 of the 98 cases of breast cancer; of these, all 3 $TPOAb^+$ women were positive for estrogen receptor and 18 of the 20 women without TPOAb.

Cross-sectional study

At the time of the EPOS screening, 37 women (1.3%) had a (previous or current) diagnosis of breast cancer. The mean TSH and FT4 concentrations in women with a diagnosis of breast cancer were similar to women without breast cancer (TSH, 1.85 mU/L, SD = 2.10, versus 1.99 mU/l (SD = 4.54) (*t* test, $p > 0.1$); FT4: 15.5 pmol/L (SD = 2.4) versus 15.3 pmol/L (SD = 2.7) (*t* test, $p > 0.1$)). The univariate analysis revealed that the presence of TPOAb was significantly related to a diagnosis of breast cancer (OR 3.0; 95% CI 1.4–6.5). No other factors were significantly related to breast cancer (see Table 2). The factors shown in Table 2 were introduced in the multiple logistic regression analysis. This analysis revealed that the presence of TPOAb was independently related to a diagnosis of breast cancer at the time of screening (OR = 3.3; 95% CI 1.3–8.5); none of the other factors showed a significant relationship to breast cancer.

Prospective study

The remaining 2738 women were followed up prospectively until July 1, 2003 (Fig. 1); in total, 7 women died after a diagnosis of cancer (all types taken together), and 226 women were lost to follow up, simply due to moving away from the area. Sixty one women (2.2%) developed breast cancer. Breast cancer was diagnosed in 6 women at 1 year, in 8 women at 2 years, in 8 women at 3 years, in 11 women at 4 years, in 5 women at 5 years, in 9 women at 6 years, in 6 women at 7 years, and in 3 women at 8 years after the EPOS screening, respectively. The women with a diagnosis of breast cancer within 1 year of screening ($n = 6$) were excluded from the analysis because signs or symptoms of breast cancer might have been present at the time of screening. Self-reported hypothyroidism and the use of thyroid medication in 1994 were associated with a previous diagnosis of breast carcinoma (including *in situ*) ≥1 year later (OR = 3.8; 95% CI 1.3–10.9, and OR = 3.2; 95 %CI 1.0–10.7, respectively). After exclusion of all women on thyroid medication, women with breast cancer ≥ 1 year after screening had lower levels of FT4 compared to those without breast cancer (*t*-test, t = 2.4; $p < 0.02$). FT4 in the lowest tenth percentile (FT4 <12.5 pmol/L) was associated with an increased risk of

TABLE 1. CHARACTERISTICS OF WOMEN 47–54 YEARS OF AGE WITHOUT ($TPOAb^-$; $n = 2,497$) and with ($TPOAb^+$; $n = 278$) TPOAb at the Time of the EPOS Screening in 1994

	$TPOAb^-$ number (%)	*$TPOAb^+$ number (%)*
Education (years) ($n = 1,997$)	9.5 years (SD = 2.5)	9.3 (SD = 2.6)
Currently smoking ($n = 2,156$)	701 (36.2)	56 (25.7) $p < 0.003$
Alcohol use (at some time) ($n = 2,453$)	2,207 (77.2)	178 (72.4) $p = 0.004$
Parity (≥1 child) ($n = 2,459$)	1,937 (87.5)	220 (89.4)
Mean number of children ($n = 2,775$)	1.9 (SD = 1.1)	1.9 (SD = 1.0)
Estrogen use (at some time) ($n = 2,467$)	1900 (85.5)	208 (84.6)
Thyroid medication ($n = 2,775$)	40 (1.6)	12 (4.3) $p < 0.001$
Menarche <13 years ($n = 2,431$)	351 (16.0)	32 (13.2)
Ovariectomy (one or both) ($n = 2,436$)	161 (7.3)	10 (4.1) $p = 0.045$
Subclinical thyroid dysfunction[a] ($n = 2,560$)	107 (4.6)	52 (20.6) $p < 0.001$
Clinical thyroid dysfunction[b] ($n = 2,560$)	9 (0.4)	9 (3.6) $p < 0.001$
Positive family history of breast cancer ($n = 1,707$)	320 (20.8)	30 (17.9)
Breast cancer[c] ($n = 2,775$)	78 (3.0)	14 (5.4)

[a]Subclinical thyroid dysfunction: abnormal TSH, normal FT4.
[b]Clinical thyroid dysfunction: both abnormal TSH and FT4.
[c]Breast cancer: previously ($n = 37$) and during follow up ($n = 56$)

Table 2. Univariate Analysis of Risk Estimates of Factors Possibly Associated with Breast Cancer

	Cross sectional[a] *OR (95%CI)*	*Prospective*[b] *OR (95%CI)*
Alcohol use	0.7 (0.4–1.7)	1.3 (0.7–2.2)
Smoking	1.4 (0.7–2.8)	1.0 (0.5–1.8)
Parity ≥1	1.2 (0.4–3.3)	1.3 (0.5–3.2)
Estrogen use[c]	1.4 (0.5–4.1)	**4.1 (1.0–16.7)**
Menarche <13 years	1.0 (0.5–1.9)	1.0 (0.6–1.9)
Positive family history of breast cancer	2.0 (0.8–4.7)	1.3 (0.6–2.9)
Subclinical thyroid dysfunction	1.2 (0.7–2.1)	1.9 (0.8–4.9)
Clinical thyroid dysfunction	Too few cases	Too few cases
Thyroid medication	1.0 (0.5–1.8)	**3.2 (1.0–10.7)**
Low FT4[d]	0.8 (0.2–2.6)	**2.3 (1.2–4.6)**
Low TSH[e]	1.6 (0.6–4.1)	**2.9 (1.5–5.7)**
TPOAb+[f]	**3.0 (1.41–6.46)**	1.1 (0.4–2.7)

Two separate analyses were performed: cross-sectional (n = 2,775; 37 women with previous breast cancer included) and prospective (n = 2,738; 56 women with new breast cancer included).
[a]Cross-sectional: at the time of screening in 1994.
[b]Prospective: during the follow up, 1994–July, 2002.
[c]Estrogen use: at some time, including OACs.
[d]Low FT4: ≤10 percentile, women on thyroid medication excluded.
[e]Low TSH: ≤ 10 percentile, women on thyroid medication excluded.
[f]TPOAb$^+$: positive for thyroid peroxidase antibodies in 1994.

breast cancer (OR = 2.3; 95% CI 1.2–4.6). These women showed concentrations of TSH within the normal range. Figure 2 shows the scatter plots of FT4 in relation with log-TSH for women without breast cancer during follow up, for women with breast cancer ≤ 3 years and for women with breast cancer > 3 years after screening, respectively. Women with breast cancer ≤3 years had lower FT4 levels (72% had FT4 below the median of 15.1 pmol/L for women without breast cancer). Also, log-TSH and FT4 were not correlated in these women (r = 0.02; n.s.; see Fig. 2).

The presence of TPOAb in 1994 was not associated with the development of new (*in situ*) breast carcinoma during the follow-up period (OR = 1.1; 95% CI 0.4–2.7). A significant relationship between the use of estrogens and the development of breast cancer was found (Table 2). It was not possible to distinguish between the type and dose of estrogens, nor the duration of use. Multiple logistic regression analysis showed that the use of estrogens (OR = 4.5; 95% CI 1.1–18.7, self-reported hypothyroidism (OR = 4.1; 95% CI 1.4–12.0), and low FT4 (OR = 2.4; 95% CI 1.2–4.9) were independently related to new breast cancer. Again, no association was found between TPOAb and the development of breast cancer.

Discussion

This is the first prospective study to describe low levels of FT4 as being an independent risk factor for the development of breast cancer in an unselected cohort of peri- and postmenopausal women. Also, hypothyroidism appeared to be associated with an increased risk for the development of breast cancer. In addition, we showed that the presence of TPOAb was more prevalent in women with a current or previous diagnosis of breast cancer. However, in a prospective study, we found that the presence of TPOAb was not related to the development of breast cancer.

In The Netherlands, the prevalence of TPOAb in women aged from 20 to 55 years is 10–13%, which is similar to that in other western countries (14,18–21). The prevalence of TPOAb in women with breast cancer was 15.2%, which is in agreement with the studies of Giani et al. and Rasmusson et al. (9,10). However, Shering et al. and Smyth et al. found higher percentages of TPOAb positivity (up to 34% compared to 18% in controls) (8,11). This is probably the result of the use of a more sensitive TPOAb test or because of the use of different cut-off points for elevated TPOAb concentrations. The point-prevalence of untreated thyroid dysfunction (for both hyper- and hypothyroidism) was 0.7%; it is not known whether these women had any signs or symptoms of thyroid dysfunction. TPOAb$^+$ women had significantly higher concentrations of TSH. This is in agreement with the results of various other studies that showed that women with elevated TSH, alone or in combination with TPOAb, are at high risk for developing (clinical) hypothyroidism (18,19,22).

Both the incidence of breast cancer (including *in situ* carcinoma) of 278/100,000/year (61 new cases in an 8-year follow up of 2,739 women) and the cumulative incidence of 3.5% (98 cases in 2,775 women with a mean age of ±60 years) were in accordance with the regional incidence (about 274/100,000 per year in women aged from 55 to 60 years) (1).

An association between the presence of TPOAb and breast cancer was also found by various other authors (5,7,9,10,12). However, these studies were cross sectional and were performed in selected populations (e.g., in patients already diagnosed as having breast cancer), and therefore it was not possible to establish a possible etiological relationship. In the prospective part of our study, we showed that the development of breast cancer was not related to the presence of TPOAb, alone or in combination with high concentrations of TSH, during an 8-year follow-up period. Therefore, we argue that a relationship between thyroid autoimmunity and

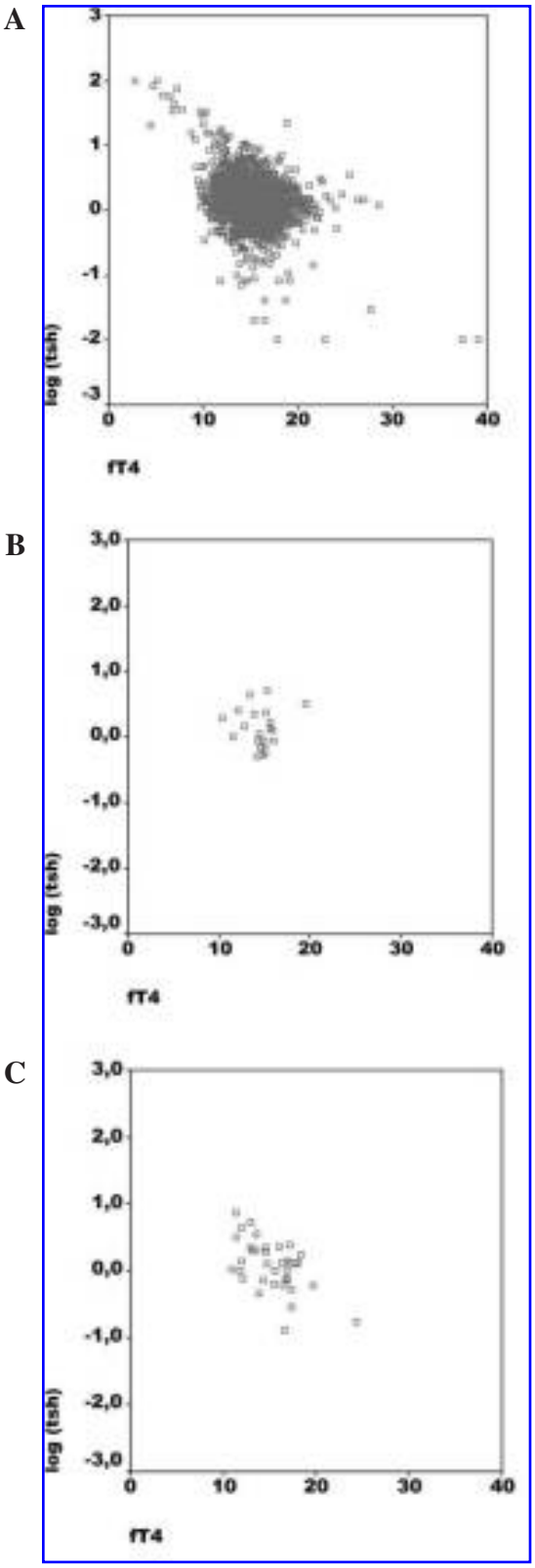

FIG. 2. Scatter plots of FT4 and log-TSH (women on thyroid medication excluded). (**A**) Women who never had breast cancer. ($n = 2404$; $r = -0.34$, $p < 0.001$). (**B**) Women with breast cancer diagnosed 1–3 years after screening ($n = 21$; $r = 0.02$, n.s.). (**C**) Women with breast cancer > 3 years after screening ($n = 31$; $r = -0.56$, $p < 0.001$).

breast cancer is unlikely. This is in conformity with the findings of Hedley et al. who, in a prospective study (with a followup of 1–11 years) of 2,523 patients with various thyroid disorders (mostly autoimmune diseases), found no indications for an increased risk of breast cancer (13).

What is the explanation for the association between TPOAb and breast cancer at a cross-sectional level? The presence of TPOAb (without increased TSH) is probably the first sign of an irradiation- and/or chemotherapy-induced thyroiditis triggering an autoimuune reaction (23). Also, an immune response of the tumor itself might explain the presence of TPOAb. Thyroid dysfunction (especially hypothyroidism) during the long-term follow up for cancers of the head and neck region and the breast has been described by several authors (24–27). The cumulative incidence of (subclinical) hypothyroidism was about 50% after a 20-year follow-up period (25,26.). It might be suggested that women treated for breast cancer with radiotherapy alone or in combination with chemotherapy should have routine thyroid function testing during follow up. Another explanation is that the stress of a breast cancer diagnosis has effect on the immune system (14).

Both self-reported hypothyroidism (OR = 3.8; 95% CI 1.3–10.9) and the use of thyroid medication (OR = 3.2; 95% CI 1.0–10.7) were associated with an increased risk of breast cancer. Smyth also suggested an association between hypothyroidism (irrespective of thyroid autoimmunity) and breast cancer (28). However, there is still no explanation for this possible association. Is seems unlikely that thyroid medication is a risk factor for the development of breast cancer because, in the majority of cases, this medication consisted of L-thyroxine replacement therapy. Thyrostatic drugs might be carcinogenic. However, to be able to establish a causative relationship, the follow-up period appeared to be too short. Also, in our study, we found no relationship between self-reported hyperthyroidism and breast cancer.

We have found that low levels of FT4 (within the tenth percentile; <12.5 pmol/L) were associated with an increased risk for breast cancer (OR = 2.3; 95% CI 1.2–4.6). This association appeared to be independent of thyroid autoimmunity, due to the absence of a relationship with TPOAb positivity and high or elevated levels of TSH (as a sign of decreased thyroid reserve). Also, we found indications of a mild disturbance of the relationship of FT4 and log-TSH in the first 1–3 years of the follow-up period (Fig. 2B). Several explanations for these findings can be suggested: Some of the women at risk for breast cancer could also have a different set point for their thyroid (relatively low FT4 in combination with low-normal TSH) without any clinical signs (29). There may be a combined genetic predisposition for hypothyroidism or low FT4 and breast cancer may exist (28), or an as yet not diagnosed but detectable breast carcinoma might lead to a mild form of non-thyroidal illness syndrome (30), or an environmental or dietary factor (such as deficient intake of iodine) may be involved (28).

In a small group of breast cancer patients, we found no relationship between TPOAb and the presence of estrogen receptors in the tumor. This was also the finding of Giani et al. (10). However, our results are not conclusive because of the small numbers.

Some limitations of this study should be mentioned. In-

formation regarding self-reported thyroid dysfunction and medication use might have biased the results of our study. Although the possible role of confounding factors was investigated by using multiple logistic regression analysis, in which other factors known from the literature to be related to breast cancer were included, it is still possible that the relationship between breast cancer and TPOAb, at a cross-sectional level, is mediated by an unknown factor. Moreover, we did not evaluate the development of TPOAb in the follow-up period prospectively, although the number of women who might develop elevated TPOAb levels during a 7-year follow-up period will be rather low. Epidemiological studies in the Netherlands have shown that the prevalence of TPOAb in women remained stable at around 10% as from about 20 years of age (20). Another limitation to this study is the relatively short follow-up period: New breast cancer resulting from TPOAb may not be detectable after a maximum of only 7 years. Finally, other indices of autoimmunity in relation to the development of breast cancer were not taken into account.

In any future research, prospective studies should be performed to evaluate whether the presence of TPOAb develops before or after the development of (detectable) breast cancer. Moreover, studies to clarify the origins of TPOAb in breast cancer patients, their potential effect on the prognosis of breast cancer, and their effect on thyroid function should be performed.

Conclusions

A relationship may exist between low levels of FT4 and the detection of breast cancer in peri- and postmenopausal women. The presence of TPOAb is a marker for the presence of breast cancer. A direct association between thyroid autoimmunity and breast cancer is unlikely. Further studies are needed to clarify the origins of the possible relationship between low FT4 and breast cancer.

References

1. Coebergh JWW, Janssen-Heijnen MLG, Louwman WJ, Voogd AC (eds) 2001 Cancer incidence, care and survival in the South of the Netherlands, 1995-1999: a report of the Eindhoven Cancer Registry with cross-border implications. Comprehensive Cancer Centre South (IKZ), Eindhoven.
2. Schernhammer ES, Laden F, Speizer FE, Willett WC, Hunter DJ, Kawachi I, Colditz GA 2001 Rotating night shifts and risk of breast cancer in women participating in the Nurses' Health Study. J Natl Cancer Inst **93:**1563–1568.
3. Hamajima N, Hirose K, Tajima K et al. 2002 Alcohol, tobacco and breast cancer: collaborative reanalysis of individual data from 53 epidemiological studies, including 58,515 women with breast cancer and 95,067 women without the disease. Br J Cancer **87:**1234–1245.
4. Chen WY, Colditz GA, Rosner B, Hankinson SE, Hunter DJ, Manson JE, Stampfer MJ, Willett WC, Speizer FE 2002 Use of postmenopausal hormones, alcohol, an risk for invasive breast cancer. Ann Intern Med **137:**798–804.
5. Kilbane MT, Ajjan RA, Weetman AP, Dwyer R, McDermott EWM, O'Higgins NJ, Smyth PPA 2000 Tissue Iodine content and serum-mediated 124I uptake-blocking activity in breast cancer. J Clin Endocrinol Metab **85:**1245–1250.
6. Tazebay UH, Wapnir IL, Levy O, Dohan O, Zuckier LS, Zhao QH, Deng HF, Amenta PS, Fineberg S Pestell RG, Carrasco N 2000 The mammary gland iodide transporter is expressed during lactation and in breast cancer. Nature Med **8:**859–860.
7. Smyth PP 1993 Thyroid disease and breast cancer. J Endocrinol Invest **16:**396–401.
8. Shering SG, Zbar AP, Moriarty M, McDermott EW, O'Higgins NJ, Smyth PP 1996 Thyroid disorders and breast cancer. Eur J Cancer Prev **5:**504–505.
9. Rasmusson B, Feldt-Rasmussen U, Hegedus L, Perrild H, Bech K, Hoier-Madsen M 1987 Thyroid function in patients with breast cancer. Eur J Cancer Clin Oncol **23:**553–556.
10. Giani C, Fierabracci P, Bonacci R, Gigliotti A, Campani D, DeNegri F, Cecchetti D, Martino E, Pinchera A 1996 Relationship between breast cancer and thyroid disease: relevance of autoimmune thyroid disorders in breast malignancy. J Clin Endocrinol Metab **81:**990–994.
11. Smyth PPA, Shering SG, Kilbane MT, Murray MJ, McDermott EWM, Smith DF, O'Higgins NJ 1998 Serum thyroid peroxidase antibodies, thyroid volume, and outcome in breast carcinoma. J Clin Endocrinol Metab **83:**2711–2716.
12. Turken O, Narln Y, Demirbas S, Onde ME, Sayan O, Kandemir EG, Yaylaci M, Ozturk A 2003 Breast cancer in association with thyroid disorder. Breast Cancer Res **5:**R110–R113.
13. Hedley AJ, Jones SJ, Spiegelhalter DJ, Clements P, Bewsher PD, Simpson JG, Weir RD 1981 Breast cancer in thyroid disease: fact or fallacy? Lancet **I(8212):**131–133.
14. Pop VJ, Maartens LH, Leusink G, Son MJ van, Knottnerus AA, Ward AM, Metcalfe R, Weetman AP 1998 Are autoimmune thyroid dysfunction and depression related? J Clin Endocrinol Metab **83:**3194–3197.
15. Smeets-Goevaers CG, Leusink GL, Papapoulus SE, Maartens LW, Keyzer JJ, Weerdenburg JP, Beijers LM, Zwinderman AH, Knottnerus JA, Pols HA, Pop VJ 1998 The prevalence of low bone mineral density in Dutch perimenopausal women: The Eindhoven perimenopausal osteoporosis study. Osteoporos Int **8:**404–409.
16. Wiersinga WM, Podoba J, Srbecky M, Van Vessem M, Van Beeren HC, Platvoet-ter Schiphorst MC 2001 A survey of iodine intake and thyroid volume in Dutch schoolchildren: reference values in an iodine-sufficient area and the effect of puberty. Eur J Endocrinol **144:**595–603.
17. Rees-Wortelboer MM, Schröder van der Elst JP, Lycklama A, Van der Heide D 1987 Iodine and goiter in the Netherlands. Ned Tijdschr Geneeskd **131:**1821–1824 (in Dutch).
18. Geul KW, Van Sluisveld ILL, Grobbee DE, Docter R, Bruyn AM de, Hooykaas H, Merwe JP van der, Hemert AM van, Krenning EP, Hennemann G, Weber RFA 1993 The importance of thyroid microsomal antibodies in the development of elevated TSH in middle-aged women: associations with serum lipids. Clin Endocrinol (Oxf) **39:**275–280.
19. Vanderpump MPJ, Tunbridge WMG, French JM, Appleton D, Bates D, Clark F, Grimley Evans J, Hasan DM, Rodgers H, Tunbridge F, Young ET 1995 The incidence of thyroid disorders in the community: a twenty-year follow up of the Whickham Survey. Clin Endocrinol (Oxf) **43:**55–68.
20. Kuijpens JL, Pop VJ, Vader HL, Drexhage HA, Wiersinga WM 1998 Prediction of post partum thyroid dysfunction: can it be improved? Eur J Endocrinol **139:**36–43.
21. Muller AF, Drexhage HA, Berghout A 2001 Postpartum thyroiditis and autoimmune thyroiditis in women of childbearing age: recent insights and consequences for antanatal and postnatal care. Endocr Rev **22:**605–630.
22. Huber G, Staub JJ, Meier C, Mitrache C, Guglielmetti M, Huber P, Braverman LE 2002 Prospective study of the spontaneous course of subclinical hypothyroidism: prognostic

value of thyrotropin, thyroid reserve, and thyroid antibodies. J Clin Endocrinol Metab **87:**3221–3226.
23. Pacini F, Vorontsova T, Molinaro E, Kuchinskaya E, Agate L, Shavrova E, Astachova L, Chiovato L, Pinchera A 1998 Prevalence of thyroid autoantibodies in children and adolescents from Belarus exposed to the Chernobyl radioactive fallout. Lancet **352:**763–766.
24. Bruning P, Bonfrer J, Jong-Bakker M de, Nooyen W, Brugers M 1985 Primary hypothyroidism in breast cancer patients with irradiated supraclavicular lymph nodes. Br J Cancer **51:**659–663.
25. Hancock SL, Cox RS, McDougall IR 1991 Thyroid diseases after treatment of Hodgkin's disease. N Engl J Med **325:**599–605.
26. Peerboom PF, Hassink EA, Melkert R, DeWit L, Nooijen WJ, Bruning PF 1992 Thyroid function 10-18 years after mantle field irradiation for Hodgkin's disease. Eur J Cancer **28A:** 1716–1718.
27. Turner SL, Tiver KW, Boyages SC 1995 Thyroid dysfunction following radiotherapy for head and neck cancer. Intern J Radiat Oncol Biol Phys **31:**427–429.
28. Smyth PPA 1997 The thyroid and breast cancer: a significant association? Ann Med **29:**1989–1991.
29. Andersen S, Pedersen KM, Bruun NH, Laurberg P 2002 Narrow individual variations in serum T4 and T3 in normal subjects: a clue to the understanding of subclinical thyroid disease. J Clin Endocrinol Metab **87:**1068–1072.
31. Langton JE, Brent GA 2002 Non thyroidal illness syndrome: evaluation of thyroid function in sick patients. Endocrinol Metab Clin North Am **31:**159–172.

Address reprint requests to:
Dr. V.J.M. Pop
Tilburg University
P.O. Box 90153
5000 LE Tilburg
The Netherlands

E-mail: v.j.m.pop@uvt.nl

This article has been cited by:

1. Robert C Smallridge. 2006. Thyroid autoimmunity and breast cancer—cause or effect?. *Nature Clinical Practice Endocrinology &#38 Metabolism* **2**:12, 660. [CrossRef]